Research Article

Cancer Epidemiology, Biomarkers & Prevention

The Effect of Patient and Contextual Characteristics on Racial/Ethnic Disparity in Breast Cancer Mortality

Richard Sposto[1,2], Theresa H.M. Keegan[3], Cheryl Vigen[1], Marilyn L. Kwan[4], Leslie Bernstein[5], Esther M. John[6,7,8], Iona Cheng[6,7], Juan Yang[6], Jocelyn Koo[6], Allison W. Kurian[7,8], Bette J. Caan[4], Yani Lu[5], Kristine R. Monroe[1], Salma Shariff-Marco[6,7,8], Scarlett Lin Gomez[6,7,8], and Anna H. Wu[1]

Abstract

Background: Racial/ethnic disparity in breast cancer–specific mortality in the United States is well documented. We examined whether accounting for racial/ethnic differences in the prevalence of clinical, patient, and lifestyle and contextual factors that are associated with breast cancer–specific mortality can explain this disparity.

Methods: The California Breast Cancer Survivorship Consortium combined interview data from six California-based breast cancer studies with cancer registry data to create a large, racially diverse cohort of women with primary invasive breast cancer. We examined the contribution of variables in a previously reported Cox regression baseline model plus additional contextual, physical activity, body size, and comorbidity variables to the racial/ethnic disparity in breast cancer–specific mortality.

Results: The cohort comprised 12,098 women. Fifty-four percent were non-Latina Whites, 17% African Americans, 17% Latinas, and 12% Asian Americans. In a model adjusting only for age and study, breast cancer–specific HRs relative to Whites were 1.69 (95% CI, 1.46–1.96), 1.00 (0.84–1.19), and 0.52 (0.33–0.85) for African Americans, Latinas, and Asian Americans, respectively. Adjusting for baseline-model variables decreased disparity primarily by reducing the HR for African Americans to 1.13 (0.96–1.33). The most influential variables were related to disease characteristics, neighborhood socioeconomic status, and smoking status at diagnosis. Other variables had negligible impact on disparity.

Conclusions: Although contextual, physical activity, body size, and comorbidity variables may influence breast cancer–specific mortality, they do not explain racial/ethnic mortality disparity.

Impact: Other factors besides those investigated here may explain the existing racial/ethnic disparity in mortality. *Cancer Epidemiol Biomarkers Prev; 25(7); 1064–72. ©2016 AACR.*

Introduction

There are well-described differences in breast cancer mortality by race and ethnicity in the United States. For example, breast cancer mortality rates were similar for African Americans and non-Latina Whites (NL Whites) in the United States until the late 1970s, but these rates began to diverge in the early 1980s (1–3). Reasons for racial/ethnic differences in mortality after breast cancer diagnosis are not completely understood. Demographic, screening, disease characteristics (4), socioeconomic and lifestyle factors (5–7), adequacy of treatment (8–13), presence of comorbidities (14, 15), neighborhood factors (16), differential influence of tumor biology on outcome (17, 18), and patient hematologic traits (19) have been cited or investigated as possibly accounting for these observed disparities. Irrespective of race and ethnicity, history of comorbidity (20, 21), and lifestyle factors such as body size and physical activity (22–27) have been shown to influence breast cancer–specific mortality, albeit not in all studies (28). Most of these previous studies were conducted in NL Whites only. Few studies have investigated the combined roles of clinical, lifestyle, and contextual factors [i.e., those related to socioeconomic and manmade ("built") physical attributes of an individual's surroundings; refs. 29, 30] in relation to breast cancer–specific mortality.

We have previously reported on the role of institutional and neighborhood contextual factors (31, 32), low physical activity (33), large body size (34), and comorbidities (35) in relation to mortality following breast cancer diagnosis in the large California Breast Cancer Survivorship Consortium (CBCSC) study, which comprised 12,210 invasive breast cancer cases diagnosed between 1993 and 2007 (36). Our objective in the current analysis was to investigate the contribution of each of these four domains of risk factors to the apparent racial/ethnic disparity in breast

[1]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California. [2]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Los Angeles, California. [3]Division of Hematology and Oncology, Department of Internal Medicine, UC Davis Comprehensive Cancer Center, Sacramento, California. [4]Division of Research, Kaiser Permanente Northern California, Oakland, California. [5]City of Hope, Duarte, California. [6]Cancer Prevention Institute of California, Fremont, California. [7]Stanford Cancer Institute, Stanford, California. [8]Stanford University School of Medicine, Stanford, California.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Richard Sposto, Children's Hospital Los Angeles, 4650 Sunset Blvd., MS#54, Los Angeles, CA 90027-6016. Phone: 323-361-8582; Fax: 323-361-7128; E-mail: rsposto@chla.usc.edu

doi: 10.1158/1055-9965.EPI-15-1326

cancer–specific mortality within the context of a single baseline model that included common demographic, clinical, and disease characteristics.

Materials and Methods

The California Breast Cancer Survivorship Consortium

The CBCSC, established in 2011, pooled data from six California-based studies to investigate racial/ethnic disparities in mortality (36). They included the Asian American Breast Cancer Study (AABCS), the Women's Contraceptive and Reproductive Experiences study (CARE), the San Francisco Bay Area Breast Cancer Study (SFBCS), the Life after Cancer Epidemiology study (LACE), the California Teachers Study (CTS), and the Multiethnic Cohort study (MEC). The CBCSC harmonized and pooled interview information from breast cancer cases and linked this information with neighborhood data from the California Neighborhoods Data System (29), data on characteristics of the primary reporting hospitals, and corresponding clinical characteristics and mortality data from the California Cancer Registry for cases diagnosed with primary invasive breast cancer between 1993 and 2007 (36). Additional methodologic details of the construction of the cohort are included in Supplementary Methods. The protocols for the CBCSC study were approved by the institutional review boards of all participating institutions and by the California State Committee for the Protection of Human Subjects.

Statistical analysis

We used a previously developed (36) Cox multiple regression model as the starting point for examining the contribution of individual disease and patient characteristics to the observed racial/ethnic disparity in breast cancer–specific mortality. This model, which we refer to as the baseline model, used the attained age time scale, was stratified by study, and included racial/ethnic group, age at diagnosis as a continuous variable on both the natural and log scales, and clinical and demographic variables that contributed significantly to predicting breast cancer–specific mortality. The baseline model variables are listed in Supplementary Table S1 and further details of its development are described in the Supplementary Methods. The CBCSC included four exposure domains: contextual factors (31, 32), physical activity (33), body size (34), and comorbidity (35) to investigate their roles in breast cancer-specific and overall mortality. For this analysis, we selected representative variables that were found to be predictive of outcome in these analyses as exposures of interest.

We performed several types of analyses in the baseline model to assess the influence of individual clinical and lifestyle factors on the racial/ethnic disparity in breast cancer–specific mortality. A univariable analysis started with the racial/ethnic group variable alone in a Cox regression model adjusted for continuous age at diagnosis and stratified by study. The remaining variables in the baseline model (Supplementary Table S1) were included individually, one by one in turn, and the resulting changes in the HR between African Americans, Latinas, and Asian Americans versus NL Whites were described. A multivariable analysis started with all variables in the model, and the change in HR of each racial/ethnic group was noted when variables were removed, individually, one by one in turn. These two analyses reveal slightly different information about the influence of the different variables. The univariable analysis identifies variables that by themselves have a large influence on HR, although if they are highly correlated with other variables these also would have similar influence on HR in this analysis. The multivariable analysis identifies variables that have, by themselves and without regard to other variables, a large influence on racial/ethnic disparity. In this analysis, removing a variable that is correlated with other variables in the model will have a smaller influence on HR, because some of the information it contains remains in the model through the remaining correlated variables. In addition, a sequential analysis was performed, starting again with the racial/ethnic group variable alone in the model, and adding individual variables in a stepwise fashion in the order of their univariable significance. This analysis assesses the change in HR as more and more variables are added, with larger changes in HR occurring whenever the first influential variable in a correlated set or an individual influential uncorrelated variable is added. Tests of significance of a single variable or sets of variables of interest when added to a reference Cox model were based on the Cox partial likelihood ratio test.

We repeated these three analyses to investigate the further influence of contextual, physical activity, body size, and comorbidity-related factors. The difference in these additional analyses was that the starting, reference model included all of the variables in the original baseline model. We also restricted these analyses to subgroups of the cohort that included only breast cancer cases from individual studies that collected data relevant to each of these four domains, as will be described below.

The measure that we devised to summarize the racial/ethnic disparity in breast cancer–specific mortality for a particular model was $D = \sqrt{\frac{\sum n_i \{\beta_i - \overline{\beta}_\bullet\}^2}{\sum n_i}}$, the sample-size weighted standard deviation of $\log_e$ HR estimates for racial/ethnic groups from the model. Here β_i is the $\log_e$ HR estimate (i.e., the Cox regression coefficient) for the ith racial/ethnic group, n_i is the racial/ethnic group sample size, and $\overline{\beta}_\bullet$ is the sample-size weighted mean of the β_i. D is independent of which group is chosen as the reference group and will be closer to zero for models where there is a smaller difference in breast cancer–specific mortality HR across the racial/ethnic groups.

To assess relative changes in this disparity measure, define D_0 as the total disparity in a reference model. For the analyses of variables in the original baseline model, D_0 was computed from a model that included only the racial/ethnic group variable, stratified by study and adjusted for age, but with no other variables from the baseline model included. For the analysis of variables related to contextual, physical activity, body size, and comorbidity factors, D_0 was computed from a model that included all of the original baseline model variables. The relative influence of a particular variable on the disparity across racial/ethnic groups in the context of one of these reference models was defined as $\frac{D_- - D_+}{D_0} \times 100$, that is, the percent of the total disparity that is contributed by the variable, where D_+ and D_- denote the disparity measures for models that do and do not include a variable of interest, respectively. Note that D is a general measure of disparity that will not by itself reflect complex changes in the HR between racial/ethnic groups. Therefore, we also examined changes in HR for individual racial/ethnic groups. We also devised an approximate likelihood ratio-based test of significance of change in the disparity measure D. This test, termed "disparity χ^2," is described in detail in Supplementary Methods.

All reported P values are based on two-sided tests, with $P < 0.05$ generally regarded as significant.

Results

The current analysis included 12,098 of the original 12,210 cases in CBCSC cohort—112 cases designated as "other" race/ethnicity were excluded. The cohort comprised 6,501 (54%) NL Whites, 2,060 African Americans (17%), 2,032 Latinas (17%), and 1,505 (12%) Asian Americans. Table 1 summarizes the frequency of selected variables and their distribution by racial/ethnic group, and Supplementary Table S1 shows all variables that are included in the baseline model.

Influence of variables in the baseline model

Figure 1 shows visually the analysis we conducted to examine the influence of the variables in the baseline model on the disparity in breast cancer–specific mortality across racial/ethnic groups. The top panel of Fig. 1 shows the HR for African Americans, Latinas, and Asian Americans relative to NL Whites as variables were added to the model. The left-most point, labeled "RACE" is the model with racial/ethnic group alone, stratified by study and adjusted for age at diagnosis, but without the remaining variables. In this starting model, breast cancer–specific mortality in African Americans was higher compared with NL Whites, with an HR of 1.69 (95% CI, 1.46–1.96; see Table 2, column 1), whereas Latinas had similar mortality to NL Whites (HR 1.00; 95% CI, 0.84–1.19), and Asian Americans had lower mortality compared with NL Whites (HR 0.52; 95% CI, 0.33–0.85).

The succession of points from left to right in the top panel of Fig. 1 resulted from adding each of the variables sequentially to the model in the order of their univariable significance, that is, their significance in a model that otherwise included only racial/ethnic groups with stratification by study and adjustment for age at diagnosis. The right-most point is the multivariable model that included all 14 variables shown in Supplementary Table S1 (the variables corresponding to the labels on the figures are shown in Table 3). The disparity in breast cancer–specific mortality between African Americans and NL Whites was substantially reduced by adjusting for all of these variables (HR 1.13; 95% CI, 0.96–1.33; Table 2, column 2). Although adding AJCC stage changed the HR somewhat for Latinas and Asian Americans, adjusting for all of the variables in the model had a much smaller impact than for African Americans. For Latinas, the HR decreased to 0.82 (95% CI, 0.69–0.99) in the fully adjusted model, whereas it increased slightly to 0.59 (95% CI, 0.38–0.96) in Asian Americans.

The bottom panel of Fig. 1 shows the univariable and multivariable percent relative influence of individual variables in the model, providing more information about which variables were

Table 1. Complete CBCSC cohort description by selected baseline model variables ($N = 12,098$)

	Racial/ethnic group				
Variable	**Non-Latina White**	**African American**	**Latina**	**Asian American**	**Total**
Total[a]	6,501 (54%)	2,060 (17%)	2,032 (17%)	1,505 (12%)	12,098 (100%)
AJCC stage					
Stage I	3,416 (53%)	827 (40%)	911 (45%)	729 (48%)	5,883 (49%)
Stage II	2,486 (38%)	923 (45%)	868 (43%)	629 (42%)	4,906 (41%)
Stage III	312 (5%)	143 (7%)	145 (7%)	90 (6%)	690 (6%)
Stage IV	102 (2%)	58 (3%)	34 (2%)	19 (1%)	213 (2%)
Unknown	185 (3%)	109 (5%)	74 (4%)	38 (3%)	406 (3%)
Grade					
Grade I	1,522 (23%)	280 (14%)	306 (15%)	215 (14%)	2,323 (19%)
Grade II	2,537 (39%)	639 (31%)	780 (38%)	594 (39%)	4,550 (38%)
Grade III	1,769 (27%)	874 (42%)	721 (35%)	569 (38%)	3,933 (33%)
Unknown	673 (10%)	267 (13%)	225 (11%)	127 (8%)	1,292 (11%)
Nodal positivity					
No positive nodes	4,338 (67%)	1,208 (59%)	1,244 (61%)	981 (65%)	7,771 (64%)
Positive nodes	1,984 (31%)	737 (36%)	713 (35%)	499 (33%)	3,933 (33%)
Unknown	179 (3%)	115 (6%)	75 (4%)	25 (2%)	394 (3%)
Prior tumor					
No	5,972 (92%)	1,906 (93%)	1,924 (95%)	1,445 (96%)	11,247 (93%)
Yes	529 (8%)	154 (7%)	108 (5%)	60 (4%)	851 (7%)
Neighborhood SES					
Lowest SES	201 (3%)	559 (27%)	263 (13%)	137 (9%)	1,160 (10%)
Lower-middle SES	591 (9%)	528 (26%)	402 (20%)	251 (17%)	1,772 (15%)
Middle SES	1,119 (17%)	420 (20%)	430 (21%)	288 (19%)	2,257 (19%)
Higher-middle SES	1,717 (26%)	338 (16%)	447 (22%)	376 (25%)	2,878 (24%)
Highest SES	2,657 (41%)	177 (9%)	440 (22%)	420 (28%)	3,694 (31%)
Unknown	216 (3%)	38 (2%)	50 (2%)	33 (2%)	337 (3%)
Surgery type					
No surgery	115 (2%)	98 (5%)	36 (2%)	18 (1%)	267 (2%)
Mastectomy	2,547 (39%)	843 (41%)	926 (46%)	792 (53%)	5,108 (42%)
Breast-conserving surgery	3,827 (59%)	1,116 (54%)	1,069 (53%)	693 (46%)	6,705 (55%)
Other	12 (0%)	3 (0%)	1 (0%)	2 (0%)	18 (0%)
Tumor size					
<1 cm	1,135 (17%)	235 (11%)	300 (15%)	267 (18%)	1,937 (16%)
<5 cm	4,730 (73%)	1,512 (73%)	1,495 (74%)	1,084 (72%)	8,821 (73%)
≥5 cm	346 (5%)	176 (9%)	120 (6%)	92 (6%)	734 (6%)
Unknown	290 (4%)	137 (7%)	117 (6%)	62 (4%)	606 (5%)

[a]Percentages in the "Total" row are row percentages, whereas other percentages are column percentages for the variable.

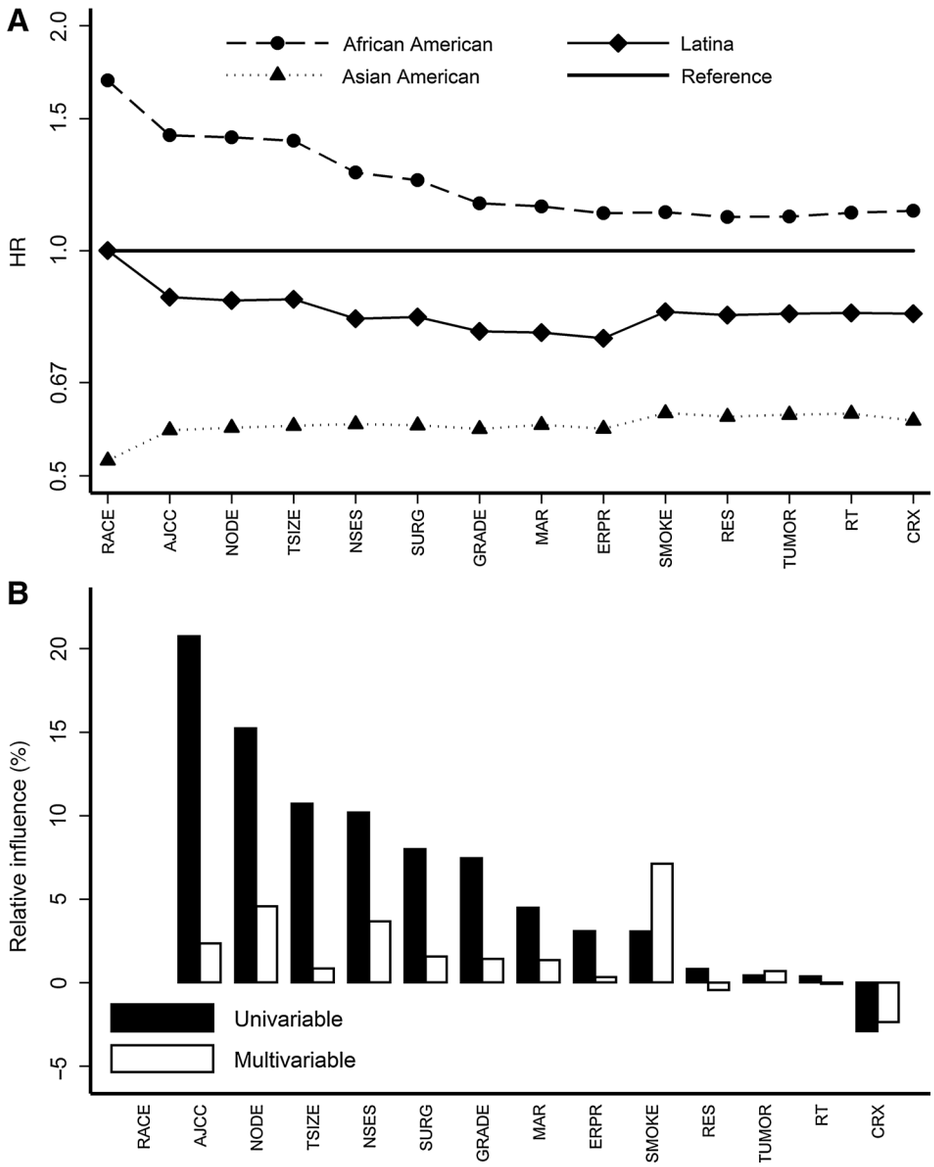

Figure 1.
A, HR for breast cancer–specific mortality of African Americans, Latinas, and Asian Americans compared to NL Whites, for a sequence of Cox regression models, the leftmost of which includes racial/ethnic group alone, stratified by study and adjusted for age at diagnosis, where variables are added in the order of their univariable significance, and where the rightmost represents the full baseline model described in ref. 36. B, univariable and multivariable relative influence of individual variables in the baseline model.

most influential in affecting racial/ethnic disparity in breast cancer–specific mortality. The variables that appeared to have the most influence are those related to disease characteristics and presentation (specifically AJCC stage, nodal involvement, tumor size, and grade, as well as surgical treatment, which is, in large part, dictated by disease presentation), neighborhood socioeconomic status (NSES), and smoking status at diagnosis. From the top panel, one sees that as variables are added to the model, the largest changes occur with AJCC stage, NSES, grade, and smoking, with AJCC stage affecting HR for all three racial/ethnic groups, NSES and grade affecting mostly African Americans and Latinas, and smoking affecting mostly Latinas and Asian Americans.

The large disparity in breast cancer–specific mortality between African Americans and NL Whites was explained to a large extent, but not completely, by the variables in this model, with comparatively smaller influence of these variables on the Latinas versus NL Whites and Asian Americans versus NL Whites disparity. The measure of disparity (D) was 40% smaller in the full model compared with the racial/ethnic group only model (Table 2, column 2, bottom), and this reduction in disparity was significant [$\chi^2(3) = 40$, $P < 0.0001$]. To examine whether this large disparity was due to the small number of cases with later-stage tumors (AJCC Stage III–IV), we repeated these analysis restricting only to the 10,789 cases with AJCC Stage I–II disease. Supplementary Table S3 and Supplementary Fig. S1 summarize these results. Interestingly, although the initial racial/ethnic groups disparity was similar to the full cohort analysis, the decrease in D from adjusting for baseline model covariates was 30% rather than 40%, due primarily to a somewhat larger remaining HR for African Americans versus NL Whites (HR 1.28; 95% CI, 1.05–1.55) in the full baseline model. HRs for Latinas and Asian Americans differed by a much smaller amount compared with the full cohort analysis.

Table 2. HR estimates and 95% confidence intervals from Cox regression analysis of breast cancer–specific mortality, for the racial/ethnic group only model versus the full baseline model

	All cases ($N = 12,098$)	
Racial/ethnic group	**Racial/ethnic group only model[a]**	**Baseline model[b]**
NL Whites	1 (Ref)	1 (Ref)
African Americans	1.69 (1.46–1.96)	1.13 (0.96–1.33)
Latina	1.00 (0.84–1.19)	0.82 (0.69–0.99)
Asian Americans	0.52 (0.33–0.85)	0.59 (0.38–0.96)
Disparity (D)	0.32	0.19
% change in D		−40%
Overall $\chi^2(df)$[c]		1,632 (64)
P[c]		<0.0001
Disparity $\chi^2(df)$[d]		40 (3)
P[d]		<0.0001

Abbreviation: *df*, degrees of freedom.
[a]Model including racial/ethnic group, and stratified by study and adjusted for age at diagnosis only.
[b]Model including racial/ethnic group and all other variables in Supplementary Table S1, stratified by study and adjusted for age at diagnosis.
[c]Cox partial likelihood ratio χ^2 comparing left model to right model in each section.
[d]Portion of the likelihood ratio χ^2 attributable to change in disparity measure (see Materials and Methods).

Clinical variables, NSES, and smoking once more had the largest influence on reducing overall disparity.

Influence of variables related to contextual factors, physical activity, body size, and comorbidity

The variables that were included for each of the four domains of interest were, for contextual factors, measures of total business count, housing crowding, urban/rural categorization, population density, commuting via public transportation, restaurant environment, traffic density, and hospital socioeconomic composition (31, 32); for physical activity, measures of activity between the ages of 10 and 19, between age 10 and diagnosis of breast cancer, and in the 10 years prior to diagnosis of breast cancer (33); for body size, prediagnosis body mass index (BMI; ref. 34); and for comorbidity, history of hypertension, diabetes, or myocardial infarction (35). Because not all of the CBCSC studies collected data relevant to the four domains of interest, the domain-specific analyses were restricted to subcohorts comprising cases from the studies with data relevant to these domains. These variables and their distribution among racial/ethnic groups within these subcohorts are described in Supplementary Table S2. Note that the subcohorts with data on contextual factors, body size, and comorbidity had similar although not identical racial/ethnic composition. The physical activity subcohort had nearly equal distributions in the racial/ethnic groups and differed from the other three subcohorts and the overall cohort because two of the three studies (CTS, LACE) not included had predominantly NL Whites. Also, this subcohort included only one study (AABCS) with Asian Americans, which prohibited estimating the HR for Asian Americans in this analysis as this category was confounded with the study stratification variable.

Table 3. List of variables and abbreviations used in figures

Variable description	**Abbreviations used in figures**
Avg. hours of activity, ages 10 to 19	ACT1
Avg. hours of activity, ages 10 to diagnosis year	ACT2
Avg. hours of activity, decade before diagnosis	ACT3
AJCC stage	AJCC
Pre diagnosis BMI	BMI
Total business count	BUSI
Commuting via public transportation	COM
Housing crowding	CRWD
Chemotherapy	CRX
Diabetes	DIAB
ER/PR status	ERPR
Grade	GRADE
Hypertension	HBP
Hospital SES composition	HSES
Marital status	MAR
Myocardial infarction	MI
Nodal positivity	NODE
Neighborhood SES	NSES
Population density	PDEN
Racial/ethnic group	RACE
Restaurant environment index	REI
Residency region	RES
Radiotherapy	RT
Smoking	SMOKE
Surgery type	SURG
Traffic density	TDEN
Tumor size	TSIZE
Prior tumor	TUMOR
Urban/rural categorization	URB

Table 4 shows the HR estimates for breast cancer–specific mortality for the four domains of interest (contextual, physical activity, body size, and comorbidity), both under the complete baseline model (left column in each section) and with the relevant domain-specific variables included (right column in each section). Note that the HR estimates in the baseline models were similar in magnitude and pattern, although not identical to, the HR estimates in the baseline model that included the full cohort (Table 2, columns 1). Hence, we think it is reasonable to use these subcohort baseline models as a reference to investigate the influence of domain-specific variables on racial/ethnic groups disparity.

The right column of each of the four sections of Table 4 shows the HR estimates when the domain-specific variables are added to the corresponding baseline model. Adding these variables had minimal further influence on the disparity in breast cancer-specific mortality across the four racial/ethnic groups. Contextual factors (those aside from NSES) and physical activity factors had a negligible effect (percent change in disparity was $<\pm 1\%$, both overall $P > 0.20$). The effects were larger when body size (percent change in disparity $= -3.70\%$, overall $P = 0.20$, disparity $P > 0.95$) and comorbidity (percent change in disparity $= -2.30\%$, overall $P = 0.003$, disparity $P > 0.95$) factors were added to the baseline models. Figure 2 shows the HR changes as variables are added sequentially to the full baseline model. This figure visually reinforces the observation that accounting for these variables has minimal influence on the residual disparity in breast cancer–specific mortality across racial/ethnic groups, even though, as in the case of the comorbidity variables, they may be significantly associated with breast cancer-specific mortality. The parallel analysis restricted to cases with stage I to II disease showed similar results (Supplementary Table S4).

Discussion

We show in this analysis of more than 12,000 breast cancer cases that individual-level patient and disease characteristics and NSES explain part (but not all) of the apparent disparity in breast

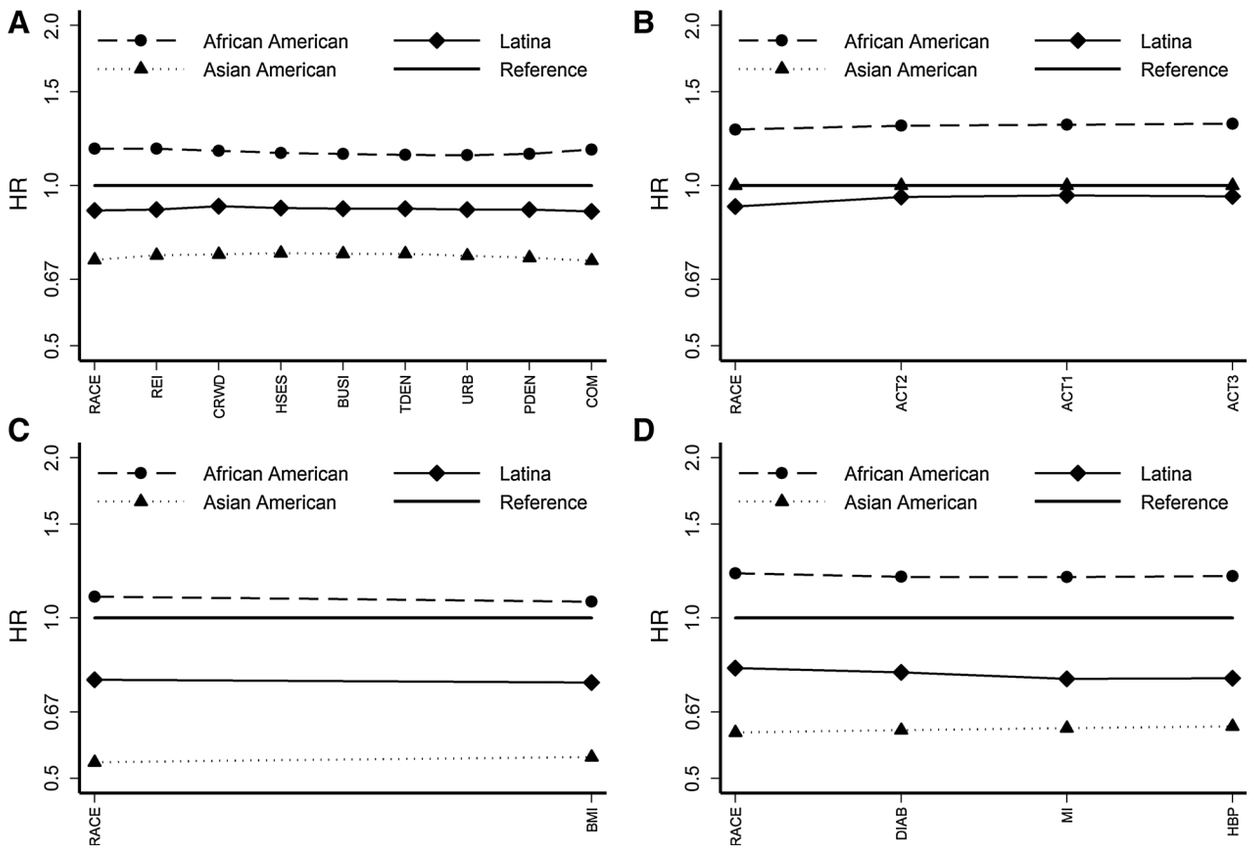

Figure 2.
Racial/ethnic group HRs for sequence of Cox regression models similar to Fig. 1, except reference is full baseline model fit to the project-specific subsamples. Contextual factors (A), physical activity (B), body size (C), and comorbidity (D).

cancer–specific mortality across different racial/ethnic groups, with disease characteristics and presentation, NSES, and smoking the most influential in explaining this disparity. Moreover, these factors have the most influence on the disparity between African Americans and NL Whites and comparatively little influence on disparities between Latinas and Asian Americans and NL Whites. In addition, we show that other contextual factors, physical activity, body size, and comorbidities apparently play a negligible role in explaining the observed racial/ethnic disparity in breast cancer–specific mortality.

Our results are in agreement with those of Curtis and colleagues (4), who used Surveillance, Epidemiology, and End Results (SEER) Medicare data on 41,020 women over 68 years of age with incident breast cancer to examine the influence of mammographic screening, tumor characteristics, tumor biology, treatment, comorbidities, and community income level on breast cancer–specific mortality between Whites, African Americans, Hispanics, and Asian and Pacific Islanders (API). The HR estimates for cancer-specific mortality from their baseline model, adjusted only for age and SEER site, for African Americans, Hispanics, and API (1.63, 1.24, and 0.59, respectively) and from their fully adjusted model (1.08, 0.88, and 0.61, respectively) are similar to the estimates from our baseline and fully adjusted models, respectively. We considered additional factors, including smoking and other lifestyle and contextual factors that were not available in their study. The association between smoking and breast cancer outcome has been reported (37, 38), and our observation that adjusting for smoking reduced the disparity between both Latinas and Asian Americans compared with NL Whites is consistent with the smaller fraction of Latinas and Asian Americans in our cohort who were smokers. The findings from both Curtis and colleagues (4) and our study suggest that the most important determinants of mortality disparity are tumor and patient characteristics and NSES, that these factors mostly affect the African Americans versus NL Whites disparity, and that comorbidities and other contextual factors, while possibly related to mortality, play a small role in explaining mortality disparity. To our knowledge, our current analysis is the first large population-based study to examine four domains of risk factors, including contextual factors, modifiable lifestyle factors (body size, physical activity), and comorbidities that appear to affect breast cancer outcome in NL Whites but that have not been studied in large numbers of women from other racial/ethnic groups.

An important strength of our analysis is that we have investigated the role of contextual factors, physical activity, body size, and comorbidity on racial/ethnic disparity in a harmonized cohort of breast cancer cases and within the context of a single multivariable baseline model. The contextual factors we studied included many additional parameters such as variables of crowding, urbanicity, street connectivity, number of businesses,

Table 4. HR estimates and 95% CIs from Cox regression analysis of breast cancer–specific mortality, for the full baseline model versus the baseline model + specific domain variables, for the subsets of cases for which domain data were available

	Contextual factors subset[a] ($N = 9,635$)		Physical activity subset ($N = 4,608$)[b]		Body size subset ($N = 11,021$)[c]		Comorbidity subset ($N = 10,106$)[d]	
Racial/ethnic group	Baseline model[e]	Baseline + domain variables[f]	Baseline model[e]	Baseline + domain variables[f]	Baseline model[e]	Baseline + domain variables[f]	Baseline model[e]	Baseline + domain variables[f]
NL White	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
African American	1.17 (0.98–1.40)	1.17 (0.98–1.40)	1.27 (1.03–1.57)	1.31 (1.06–1.61)	1.10 (0.93–1.30)	1.07 (0.90–1.27)	1.21 (1.01–1.46)	1.20 (1.00–1.44)
Latina	0.90 (0.74–1.09)	0.89 (0.73–1.09)	0.91 (0.72–1.17)	0.95 (0.74–1.22)	0.77 (0.63–0.93)	0.76 (0.62–0.92)	0.81 (0.65–1.00)	0.77 (0.62–0.96)
Asian	0.73 (0.43–1.23)	0.72 (0.43–1.23)	(omitted)	(omitted)	0.54 (0.32–0.90)	0.55 (0.32–0.93)	0.61 (0.30–1.24)	0.63 (0.31–1.27)
Disparity (D)	0.14	0.14	0.12	0.12	0.23	0.22	0.20	0.19
% Change in D		<±1%		<±1%		−3.70%		−2.30%
Overall $\chi^2(df)$[g]		31.8 (27)		8.96 (7)		3.22 (2)		20.2 (6)
p[g]		0.24		0.25		0.20		0.003
Disparity $\chi^2(df)$[h]		0.0 (3)		0.12		0.07(3)		0.16 (3)
p[h]		>0.95		[i]		>0.95		>0.95

Abbreviation: *df*, degrees of freedom.

[a]LACE excluded.

[b]Physical activity: CTS, LACE, MEC excluded.

[c]Body size: none excluded.

[d]Comorbidity: MEC excluded.

[e]Model including racial/ethnic group and all other variables in Supplementary Table S1, stratified by study and adjusted for age at diagnosis. Analysis excludes cases from studies that did not collect variables relevant to the specific domain. In addition, some cases with missing data relevant to the domain are also excluded.

[f]Includes all variables in the baseline model plus domain-specific variables.

[g]Cox partial likelihood ratio χ^2comparing left model to right model in each section.

[h]Portion of the likelihood ratio χ^2 attributable to change in disparity measure (see Materials and Methods).

[i]Could not be computed because of parameter aliasing.

restaurants, and parks (29, 32). Our study also had the limitations that the domain-specific variables were not all available in all six studies in the CBCSC. In addition, these variables were limited to exposures that occurred before diagnosis, and they may not capture complete exposure (e.g., not all possible comorbidities are included, physical activity measures did not include occupational or housework-related activity).

There are other variables that could contribute to the racial/ethnic disparity in breast cancer–specific mortality that we were not able to consider. Although we had some data on treatment, data on the appropriateness of chemotherapy, radiotherapy, or surgical treatments administered, or patient compliance with prescribed treatments and clinical follow-up, were not available. Relevant to this, within an equal-access health system with standardized practice guidelines, racial/ethnic-specific differences in the initiation of adjuvant hormonal therapy (39) and in the use of chemotherapy (11) have been reported. Results on compliance from single institution studies are less clear. Sharma and colleagues (40) evaluated compliance with radiotherapy in a large institutional series of White and African-American patients who had undergone breast conservation surgery and found no difference in the rate of compliance. In a much smaller series, Bhatta and colleagues (41) found no difference in compliance to adjuvant hormone therapy between White and Black patients with estrogen receptor–positive breast cancer. Our inclusion of factors related to NSES, which may indirectly reflect access to care, possibly captured part of any therapy compliance effect.

Genetic differences between racial/ethnic groups also have been considered. Bach and colleagues (17) synthesized a very large cohort of White and Black breast cancer patients and concluded from a meta-analysis that in comparably and appropriately treated patients, there was little difference in cancer-specific mortality between races. They concluded, therefore, that differences in cancer biology are unlikely to explain any disparity in outcome between Blacks and Whites. In contrast, Albain and colleagues (42) analyzed outcome in African Americans versus other races in more than 19,000 patients treated on Southwest Oncology Group clinical trials and concluded that, for sex-specific cancers, African Americans had worse outcome despite uniform staging, treatment, and follow-up. Genetic differences potentially can explain other disparities, such as the better outcome in Asian Americans. For example, Shimizu and colleagues (43) have reported a much lower frequency in Asians than in Caucasians of genetic polymorphisms in CYP2D6 associated with poor drug metabolism, and these have been associated with lower endoxifen levels (44) and with poorer outcome (45) in breast cancer patients treated with tamoxifen.

Dietary factors may also contribute to the observed racial/ethnic disparity in outcome. For example, Nechuta and colleagues (46) have shown that soy intake was inversely associated with breast cancer recurrence in both U.S. and Chinese women.

Bias in assessing breast cancer–specific mortality also may be a factor. For example, Gomez and colleagues (personal communication) investigated completeness of follow-up (alive and more than 2 years from the reference date December 31, 2012) in more than 500,000 cases in the CCR during the years 2000 to 2009. They found higher rates of incomplete follow-up in Asian Americans (9%) and Hispanics (6%) compared with non-

Hispanic Whites (2%). This admits the possibility that the observed better outcome in these patient groups could in part be due to bias resulting from informative censoring. In our cohort, using the same definition with our cut-off date of December 31, 2012, incomplete follow-up rates in non-Hispanic whites, Latinas, Asians, and African Americans were 2%, 4%, 5.2%, and 4.3%, respectively. Hence, the overall rate of incomplete follow-up is small in our cohort, as is the difference in these rates between racial/ethnic categories. Although this does not eliminate the theoretical possibility that differences in informative censoring may be causing bias in our results, these generally low rates of incomplete follow-up suggest that whatever bias would be very small or negligible.

In conclusion, in our analysis, the racial/ethnic disparity in breast cancer–specific mortality remains after accounting for clinical, patient, contextual, and modifiable lifestyle factors. Although some of these factors may have prevalence that is different across racial/ethnic groups, and may also be associated with breast cancer–specific mortality, this association is not strong enough to explain all of the observed racial/ethnic disparity in outcome. Other unmeasured factors, such as yet unknown underlying genetic differences, unappreciated biases in measuring racial/ethnic differences in outcome, remain to be investigated to fully explain the observed mortality differences between NL Whites, African Americans Latinas, and Asian Americans.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

Authors' Contributions

Conception and design: R. Sposto, T.H.M. Keegan, C. Vigen, E.M. John, A.W. Kurian, K.R. Monroe, S.L. Gomez, A.H. Wu

Development of methodology: R. Sposto, C. Vigen, K.R. Monroe, A.H. Wu

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Vigen, M.L. Kwan, L. Bernstein, E.M. John, J. Koo, B.J. Caan, Y. Lu, K.R. Monroe, S. Shariff-Marco, A.H. Wu

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Sposto, C. Vigen, M.L. Kwan, I. Cheng, J. Yang, J. Koo, B.J. Caan, Y. Lu, K.R. Monroe

Writing, review, and/or revision of the manuscript: R. Sposto, T.H.M. Keegan, C. Vigen, M.L. Kwan, L. Bernstein, E.M. John, I. Cheng, J. Koo, A.W. Kurian, B.J. Caan, Y. Lu, K.R. Monroe, S. Shariff-Marco, S.L. Gomez, A.H. Wu

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Vigen, L. Bernstein, J. Yang, S.L. Gomez

Acknowledgments

The authors gratefully acknowledge Dr. Brian Henderson's contribution to this research.

Grant Support

This work was supported by grants 16ZB-8001 (to A.H. Wu, R. Sposto, and C. Vigen), 16ZB-8002 (to S.L. Gomez, E.M. John, T.H.M. Keegan, A.W. Kurian, and S. Shariff-Marco), 16ZB-8003 (to L. Bernstein and Y. Lu), 16ZB-8004 (to M.L. Kwan and B.J. Caan), and 16ZB-8005 (to K. Monroe) from the California Breast Cancer Research Program. The AABCS was supported by the California Breast Research Program (CBCRP) grants 1RB-0287, 3PB-0120, and 5PB-0018 (to A.H. Wu). The SFBCS was supported by National Cancer Institute grants R01 CA63446 and R01 CA77305, by the U.S. Department of Defense (DOD) grant DAMD17-96-1-6071, and by the CBCRP grants 4JB-1106 and 7PB-0068 (to E.M. John). The Women's CARE Study was funded by the National Institute of Child Health and Human Development (NICHD), through a contract with USC (N01-HD-3-3175), and the CTS was funded by the California Breast Cancer Act of 1993; National Cancer Institute grants (R01 CA77398 and K05 CA136967; to L. Bernstein); and the California Breast Cancer Research Fund (contract 97-10500; to L. Bernstein and Y. Lu). The Multiethnic Cohort Study was supported by National Cancer Institute grants R01 CA54281, R37CA54281, and UM1 CA164973. The LACE Study is supported by National Cancer Institute grant R01 CA129059 (to B.J. Caan and M.L. Kwan). The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #1U58 DP000807-01 awarded to the Public Health Institute.

Received January 4, 2016; revised March 25, 2016; accepted March 29, 2016; published OnlineFirst April 26, 2016.

References

1. Jatoi I, Anderson WF, Rao SR, Devesa SS. Breast cancer trends among black and white women in the United States. J Clin Oncol 2005;23:7836–41.
2. Jatoi I, Becher H, Leake CR. Widening disparity in survival between white and African-American patients with breast carcinoma treated in the U.S. Department of Defense Healthcare system. Cancer 2003;98:894–9.
3. Menashe I, Anderson WF, Jatoi I, Rosenberg PS. Underlying causes of the black-white racial disparity in breast cancer mortality: a population-based analysis. J Natl Cancer Inst 2009;101:993–1000.
4. Curtis E, Quale C, Haggstrom D, Smith-Bindman R. Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? Cancer 2008;112:171–80.
5. McKenzie F, Jeffreys M. Do lifestyle or social factors explain ethnic/racial inequalities in breast cancer survival? Epidemiol Rev 2009;31:52–66.
6. Nietert PJ, Sutherland SE, Keil JE, Bachman DL. Demographic and biologic influences on survival in whites and blacks: 40 years of follow-up in the Charleston Heart Study. Int J Equity Health 2006;5:8.
7. Keegan TH, Kurian AW, Gali K, Tao L, Lichtensztajn DY, Hershman DL, et al. Racial/ethnic and socioeconomic differences in short-term breast cancer survival among women in an integrated health system. Am J Public Health 2015;105:938–46.
8. Griggs JJ, Sorbero ME, Stark AT, Heininger SE, Dick AW. Racial disparity in the dose and dose intensity of breast cancer adjuvant chemotherapy. Breast Cancer Res Treat 2003;81:21–31.
9. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med 2003;163:49–56.
10. Wright JL, Reis IM, Zhao W, Panoff JE, Takita C, Sujoy V, et al. Racial disparity in estrogen receptor positive breast cancer patients receiving trimodality therapy. Breast 2012;21:276–83.
11. Kurian AW, Lichtensztajn DY, Keegan TH, Leung RW, Shema SJ, Hershman DL, et al. Patterns and predictors of breast cancer chemotherapy use in Kaiser Permanente Northern California, 2004–2007. Breast Cancer Res Treat 2013;137:247–60.
12. Adams SA, Butler WM, Fulton J, Heiney SP, Williams EM, Delage AF, et al. Racial disparities in breast cancer mortality in a multiethnic cohort in the Southeast. Cancer 2012;118:2693–9.
13. Smith ER, Adams SA, Das IP, Bottai M, Fulton J, Hebert JR. Breast cancer survival among economically disadvantaged women: the influences of

delayed diagnosis and treatment on mortality. Cancer Epidemiol Biomarkers Prev 2008;17:2882–90.
14. Braithwaite D, Tammemagi CM, Moore DH, Ozanne EM, Hiatt RA, Belkora J, et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. Int J Cancer 2009;124:1213–9.
15. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 2005;294:1765–72.
16. Akinyemiju TF, Soliman AS, Johnson NJ, Altekruse SF, Welch K, Banerjee M, et al. Individual and neighborhood socioeconomic status and healthcare resources in relation to black-white breast cancer survival disparities. J Cancer Epidemiol 2013;2013:490472.
17. Bach PB, Schrag D, Brawley OW, Galaznik A, Yakren S, Begg CB. Survival of blacks and whites after a cancer diagnosis. JAMA 2002;287:2106–13.
18. Shiao YH, Chen VW, Scheer WD, Wu XC, Correa P. Racial disparity in the association of p53 gene alterations with breast cancer survival. Cancer Res 1995;55:1485–90.
19. Wang C, Civan J, Lai Y, Cristofanilli M, Hyslop T, Palazzo JP, et al. Racial disparity in breast cancer survival: the impact of pre-treatment hematologic variables. Cancer Causes Control 2015;26:45–56.
20. Patterson RE, Flatt SW, Saquib N, Rock CL, Caan BJ, Parker BA, et al. Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat 2010;122:859–65.
21. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285:885–92.
22. Abrahamson PE, Gammon MD, Lund MJ, Flagg EW, Porter PL, Stevens J, et al. General and abdominal obesity and survival among young women with breast cancer. Cancer Epidemiol Biomarkers Prev 2006;15:1871–7.
23. Cleveland RJ, Eng SM, Abrahamson PE, Britton JA, Teitelbaum SL, Neugut AI, et al. Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:1803–11.
24. Goodwin PJ, Boyd NF. Body size and breast cancer prognosis: a critical review of the evidence. Breast Cancer Res Treat 1990;16:205–14.
25. Keegan TH, Milne RL, Andrulis IL, Chang ET, Sangaramoorthy M, Phillips KA, et al. Past recreational physical activity, body size, and all-cause mortality following breast cancer diagnosis: results from the Breast Cancer Family Registry. Breast Cancer Res Treat 2010;123:531–42.
26. Rock CL, Demark-Wahnefried W. Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol 2002;20:3302–16.
27. West-Wright CN, Henderson KD, Sullivan-Halley J, Ursin G, Deapen D, Neuhausen S, et al. Long-term and recent recreational physical activity and survival after breast cancer: the California Teachers Study. Cancer Epidemiol Biomarkers Prev 2009;18:2851–9.
28. Sternfeld B, Weltzien E, Quesenberry CPJr, Castillo AL, Kwan M, Slattery ML, et al. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. Cancer Epidemiol Biomarkers Prev 2009;18:87–95.
29. Gomez SL, Glaser SL, McClure LA, Shema SJ, Kealey M, Keegan TH, et al. The California Neighborhoods Data System: a new resource for examining the impact of neighborhood characteristics on cancer incidence and outcomes in populations. Cancer Causes Control 2011;22:631–47.
30. Brownson RC, Hoehner CM, Day K, Forsyth A, Sallis JF. Measuring the built environment for physical activity: state of the science. Am J Prev Med 2009;36:S99–123.
31. Cheng I, Shariff-Marco S, Koo J, Monroe KR, Yang J, John EM, et al. Contribution of the neighborhood environment and obesity to breast cancer survival: the California Breast Cancer Survivorship Consortium. Cancer Epidemiol Biomarkers Prev 2015;24:1282–90.
32. Shariff-Marco S, Yang J, John EM, Kurian AW, Cheng I, Leung R, et al. Intersection of race/ethnicity and socioeconomic status in mortality after breast cancer. J Community Health 2015;40:1287–99.
33. Lu Y, John EM, Sullivan-Halley J, Vigen C, Gomez SL, Kwan ML, et al. History of recreational physical activity and survival after breast cancer: the California Breast Cancer Survivorship Consortium. Am J Epidemiol 2015;181:944–55.
34. Kwan ML, John EM, Caan BJ, Lee VS, Bernstein L, Cheng I, et al. Obesity and mortality after breast cancer by race/ethnicity: the California Breast Cancer Survivorship Consortium. Am J Epidemiol 2014;179:95–111.
35. Wu AH, Kurian AW, Kwan ML, John EM, Lu Y, Keegan TH, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). Cancer Epidemiol Biomarkers Prev 2015;24:361–8.
36. Wu AH, Gomez SL, Vigen C, Kwan ML, Keegan TH, Lu Y, et al. The California Breast Cancer Survivorship Consortium (CBCSC): prognostic factors associated with racial/ethnic differences in breast cancer survival. Cancer Causes Control 2013;24:1821–36.
37. Braithwaite D, Izano M, Moore DH, Kwan ML, Tammemagi MC, Hiatt RA, et al. Smoking and survival after breast cancer diagnosis: a prospective observational study and systematic review. Breast Cancer Res Treat 2012;136:521–33.
38. Pierce JP, Patterson RE, Senger CM, Flatt SW, Caan BJ, Natarajan L, et al. Lifetime cigarette smoking and breast cancer prognosis in the After Breast Cancer Pooling Project. J Natl Cancer Inst 2014;106:djt359.
39. Livaudais JC, Hershman DL, Habel L, Kushi L, Gomez SL, Li CI, et al. Racial/ethnic differences in initiation of adjuvant hormonal therapy among women with hormone receptor-positive breast cancer. Breast Cancer Res Treat 2012;131:607–17.
40. Sharma C, Harris L, Haffty BG, Yang Q, Moran MS. Does compliance with radiation therapy differ in African-American patients with early-stage breast cancer? Breast J 2010;16:193–6.
41. Bhatta SS, Hou N, Moton ZN, Polite BN, Fleming GF, Olopade OI, et al. Factors associated with compliance to adjuvant hormone therapy in Black and White women with breast cancer. Springerplus 2013;2:356.
42. Albain KS, Unger JM, Crowley JJ, Coltman CAJr, Hershman DL. Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group. J Natl Cancer Inst 2009;101:984–92.
43. Shimizu T, Ochiai H, Asell F, Shimizu H, Saitoh R, Hama Y, et al. Bioinformatics research on inter-racial difference in drug metabolism. I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19. Drug Metab Pharmacokinet 2003;18:48–70.
44. Lim JS, Chen XA, Singh O, Yap YS, Ng RC, Wong NS, et al. Impact of CYP2D6, CYP3A5, CYP2C9 and CYP2C19 polymorphisms on tamoxifen pharmacokinetics in Asian breast cancer patients. Br J Clin Pharmacol 2011;71:737–50.
45. Zeng Z, Liu Y, Liu Z, You J, Chen Z, Wang J, et al. CYP2D6 polymorphisms influence tamoxifen treatment outcomes in breast cancer patients: a meta-analysis. Cancer Chemother Pharmacol 2013;72:287–303.
46. Nechuta SJ, Caan BJ, Chen WY, Lu W, Chen Z, Kwan ML, et al. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. Am J Clin Nutr 2012;96:123–32.